Effects of Dietary Selenium on Mood in Healthy Men Living in a Metabolic Research Unit

Wayne Chris Hawkes and Linda Hornbostel

Eleven healthy men were confined in a metabolic research unit for 120 days in a double-blind study of the effects of dietary selenium on mood as assessed by the Profile of Mood States—Bipolar Form. At an intake of 2800 kcal/day, the diet of conventional foods provided 80 μg/day of selenium for the first 21 days, then either 13 or 356 μg/day for the remaining 99 days. There were no significant changes in any of the mood scales due to dietary selenium. However, in the low-selenium group, the changes in the agreeable–hostile and the elated–depressed subscales were correlated with initial erythrocyte selenium concentration; that is, the lower the initial selenium status, the more the mood scores decreased. These results suggest that persons with low selenium status might experience relatively depressed moods and support the idea that selenium plays a special role in the brain. However, these studies do not support the notion that selenium supplementation could promote improvements in mood in persons eating a typical U.S. diet.

Key Words: Selenium, mood, nutrition, human, profile of mood states, nutritional status

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Introduction

Selenium is a trace element essential to humans (Combs and Combs 1986) that functions in the body as the amino acid selenocysteine at the active sites of selenium-dependent enzymes (Hawkes et al 1985). Three forms of glutathione peroxidase (EC 1.11.1.9, an antioxidant enzyme) and a "type I" iodothyronine 5′-deiodinase (responsible for producing most of the active form of thyroid hormone) have been identified in humans (Stadtman 1991), but the majority of the body's selenium is in selenoproteins of unknown function. The amount of selenium in the diet is determined primarily by the concentration of selenium in the soil where foods originate and can range from as little as 11 μg/day to over 1 mg/day (Combs and Combs 1986). Such extreme intakes usually do not occur in developed countries, where the food distribution infrastructures tend to average out the geographic differences in selenium contents.

Several lines of evidence point to the suggestion that selenium may have specialized functions in the central nervous system (CNS). In rats, the brain has a higher metabolic priority for selenium than any other tissue (Burk et al 1972; Djujic et al 1992; Behne et al 1988) and is the only rat tissue that preferentially takes up selenium from a putative selenium transport protein (Burk et al 1991). Rat brain has the lowest glutathione peroxidase activity of any tissue (Behne and Wolters 1983) and selenium and glutathione peroxidase are distributed unevenly in the brain

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(Hock et al 1975; Larsen et al 1979) and its subcellular fractions (Tripp and Whanger 1984; Clausen 1991), suggesting that much of the brain selenium may be involved in other functions (Behne et al 1988). A direct link between dietary selenium and CNS function was found in a study in which high-dose selenium supplementation caused increased hyperactivity and arousal behavior in mice (Boylan et al 1990).

Serum selenium concentrations were lower in senility cases than in age-matched controls (Simonoff et al 1988) and brain selenium concentrations in Alzheimer's patients were only 60% of those in controls (Corrigan et al 1991). An antioxidant mixture supplying 200 μg/day of selenium to geriatric patients for 12 months caused a slight but progressive improvement in a clinical rating scale for dementia syndromes (Clausen et al 1989). Clinical improvements due to selenium supplementation have been reported in children with intractable seizures (Weber et al 1991) and juvenile neuronal ceroid lipofuscinosis (Westermarck 1984). Dietary selenium deficiency has been implicated as a causative factor, along with severe iodine deficiency, in the etiology of endemic myxedematous cretinism in Central Africa (Contempré et al 1991), presumably due to its role in thyroid hormone metabolism (Arthur et al 1992).

In a randomized, placebo-controlled, double-blind, crossover study of 50 British women and men, 5 weeks of supplementation with 100 μg/day of selenium was associated with an elevation in mood, as assessed by the Profile of Mood States–Bipolar Form (POMS-BI), and the degree of improvement was inversely related to the subjects' baseline selenium intake; that is, the lower the subject's selenium status, the greater the improvement in mood (Benton and Cook 1991). The present study was part of a larger study on the biochemical effects of selenium and was conducted to confirm and extend Benton and Cook's findings by testing for effects of dietary selenium on mood in subjects adapted to the higher selenium intake of a U.S. diet under the controlled conditions of a metabolic research unit.

Method

Eleven men (out of 12 originally enrolled), ages 20–45 (32.9 ± 8.2 years [SD]), completed the entire 120 day study. Subjects were of normal weight (75.5 ± 10.6 kg) and height (178 ± 5.5 cm), nonsmokers, drug and alcohol free, with normal clinical blood profiles. They were examined by a physician before admission to the study and found to be in good health. Candidates for the study gave a complete medical and psychiatric history and were interviewed by a trained staff member and by the principal investigator. Each candidate completed the Minnesota Multiphasic Personality Inventory (MMPI), which was scored and interpreted by a licensed psychologist. Based on the MMPI results, some of the candidates were subsequently interviewed by the psychologist. Individuals with current symptoms or history of psychiatric problems or treatment were eliminated. The study protocol was reviewed and approved by the Human Studies Review Committees of the University of California at Davis and the U.S. Department of Agriculture. The protocol was reviewed with the study volunteers and their informed consent was obtained prior to the study, in accordance with the Common Federal Policy for Protection of Human Research Subjects.

The subjects were confined in a metabolic research unit (two subjects to a room) for 120 days under 24-hour supervision by staff members. Subjects participated in two required 2 mile walks per day, had frequent optional outside afternoon and evening activities while escorted by staff members, and were permitted visitors, in the presence of staff escorts, for 3 hours each Sunday afternoon. Due to other investigations being conducted during this study, the subjects also underwent frequent blood draws and various other moderately invasive procedures throughout the study.

Study subjects were fed a diet composed of conventional foods and based on beef and rice as staples. To ensure an adequate intake of micronutrients, one multivitamin, multimineral supplement tablet, free of selenium (Unicap M, Upjohn Co., Kalamazoo, MI), was administered to each subject per day. The total diet was calculated to contain at least 100% of the U.S. Recommended Dietary Allowance (RDA) for all nutrients except magnesium (60% of RDA), calcium (66% of RDA), and selenium. With the exception of protein, which was kept lower than normal to help control the selenium content, the diet approximated the composition of a typical U.S. diet (54% of calories from carbohydrate, 11.5% from protein, and 34.4% from fat, with a polyunsaturated fat/saturated fat ratio of 0.83). The diet was fed in three daily meals and an evening snack, using eight different daily menus that repeated every 8 days. For the first 21 days, all subjects were fed a diet that provided 80 μg/day of selenium (U.S. RDA = 70 μg/day; NRC 1989) at a caloric intake of 2800 kcal/day to adapt the subjects to the experimental diet and the conditions of the metabolic research unit. The subjects were randomly assigned to one of two groups after being blocked into six pairs matched for blood selenium concentrations. For the remaining 99 days, one group was fed a diet that provided 13 μg/day of selenium and the other group was fed a diet that provided 356 μg/day, at caloric intakes of 2800 kcal/day. The low-selenium and high-selenium diets provided daily selenium intakes that were, respectively, lower than the estimated minimum require-

ment (17 μg/day) to protect against endemic cardiomyopathy (Keshan disease; Yang et al 1989) and approximately equal to the U.S. Environmental Protection Agency's maximum safe intake (5 μg/kg/day, "oral reference dose," Poirier and Abernathy 1992). The only difference between the experimental diets was the geographic origin of the rice and beef staples, which were obtained from regions with either very high or very low soil selenium; all other aspects of the diets were identical. The selenium contents of the diets were estimated by direct analysis of the foods (> 80% of dietary selenium) and from food composition tables (Gebhardt and Holden 1992) (< 20% of dietary selenium). Subjects and staff members were blinded to the subjects' selenium treatments (double-blind design). The subjects' caloric intakes were adjusted as needed to maintain their body weights within 2% of their initial body weights by increasing or decreasing all components of the diets proportionally. One subject in the high-selenium group voluntarily withdrew from the study on day 61 for personal reasons unrelated to the study. His data are not included.

Measurement of Mood

The Bi-Polar form of the POMS (Lorr and McNair 1984) was filled out by the subjects seven times during the study, on days 14, 21, 28, 49, 63, 91, and 105. The POMS-BI purports to measure six bipolar mood states, each defined by a subscale. The POMS-BI questionnaire consists of 72 adjectives describing moods. On a four-point scale ranging from 0 to 3, subjects indicated how well the adjectives described how they were feeling currently. Each subscale is composed of the responses to 12 adjectives, yielding a maximum possible score of 36 on each subscale. Higher numerical scores indicate less distress and specifically that a subject was feeling more clearheaded than confused; more composed than anxious; more energetic than tired; more elated than depressed; more confident than unsure; and more agreeable than hostile. Testing was initiated at day 14 to allow the subjects time to adjust to the living conditions in the metabolic research unit, so that only changes due to the diet treatments would be reflected in subsequent tests and to allow time for a second weekly measurement on day 21, before the diet treatments began. Testing was stopped at day 105 to avoid the strong response bias likely to be associated with the end of a long confinement. Subjects filled out the POMS-BI after breakfast on Sunday mornings during scheduled quiet time.

Estimates of Prestudy Dietary Selenium

Subjects recorded the types and amounts of all foods eaten for 4 days during the week immediately preceding the start of the study. Prestudy selenium intakes were estimated from the 4 day food diaries using a computerized food composition database program (Food Processor Plus, version 5, 1992, ESHA Research, Salem, OR).

Selenium Analysis

Selenium concentrations in the foods and erythrocytes were measured by a modification of the fluorometric technique (Watkinson 1966), with enhanced detection by high performance liquid chromatography (Vézina and Bleau 1988).

Statistical Analysis

The raw scores obtained for each of the six mood subscales were used without normalization. The composite score was obtained by summing the scores for the six individual subscales (Lorr and McNair 1984). Data were analyzed using BMDP Solo statistical analysis software (BMDP Statistical Software, Los Angeles, CA). A probability of 0.05 or less was considered significant.

Due to the possibility that the departure of the one subject who voluntarily withdrew from the study may have affected the mood of his roommate, all of the statistical analyses were conducted twice, with or without exclusion of that roommate. Exclusion of the roommate had no effect on the statistical significance of any of the tests. The data presented therefore include all 11 subjects who completed the study.

Results

As shown in Figures 1–7, the mean composite score and the means of the six mood subscales did not change significantly. The changes within subjects were variable, with some subjects in each selenium treatment group showing slight increases in some of the subscales, while others in each group showed decreases. There were no consistent trends in the changes of any of the subscales within either of the selenium treatment groups.

No significant effect of dietary selenium treatment could be detected on any of the six mood subscales or the composite score when the data were analyzed by repeated measures analysis of variance of all seven time points; repeated measures analysis of variance of day 14 vs. day 105; repeated measures analysis of variance of the day 14/21 averages vs. the day 63/91/105 averages; or one-way analysis of variance of the changes between the day 14/21 averages and the day 63/91/105 averages, with or without initial erythrocyte selenium concentration as a covariate. The lack of an effect of the selenium treatments

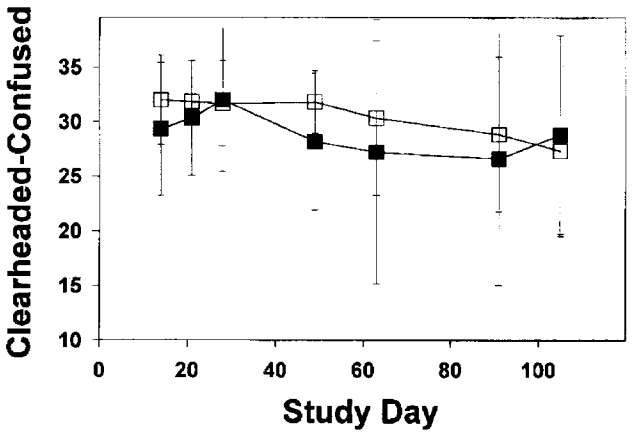

Figure 1. POMS-BI clearheaded–confused subscale scores during selenium supplementation (■) and depletion (□). The mean values of the subscale scores (± SEM) are plotted against time during the study. The POMS-BI was given on days 14, 21, 28, 49, 63, 91, and 105. All subjects received adequate selenium for the first 21 days. Dietary selenium depletion or supplementation started on day 22.

stands in sharp contrast to the results of Benton and Cook (1991), who observed significant increases in the composite score and on the composed–anxious and clearheaded–confused subscales after 5 weeks of supplementation with 100 μg/day of selenium.

Although the selenium treatments applied during this study had no discernible effects on mood, the data did reveal a significant relationship between the changes in some of the mood subscales of the subjects fed the low-selenium diet and their initial erythrocyte selenium concentrations at entry to the study, which were used as an indicator of long-term, prestudy selenium nutritional status. Table 1 shows the linear correlation coefficients between the changes in mood scores and initial erythrocyte selenium concentration. In the low-selenium group, the changes in the agreeable–hostile subscale and the elated–depressed subscale were significantly correlated with the initial erythrocyte selenium. None of the mood

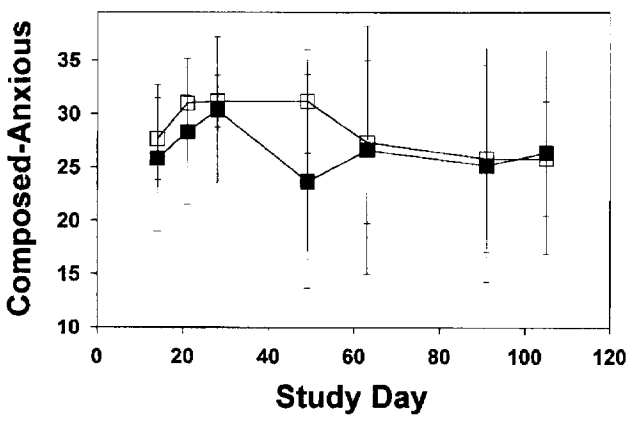

Figure 2. POMS-BI composed–anxious subscale scores during selenium supplementation (■) and depletion (□). See Figure 1.

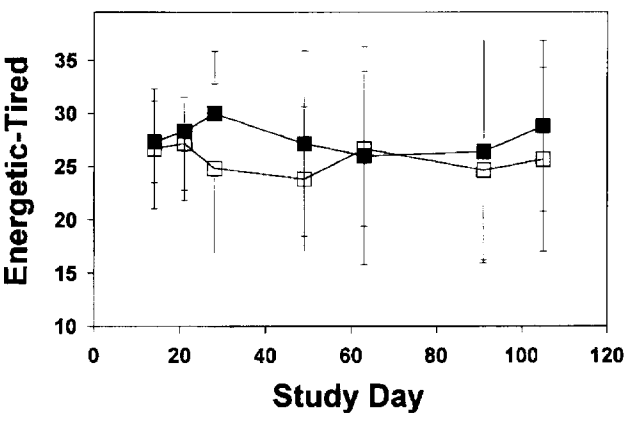

Figure 3. POMS-BI energetic–tired subscale scores during selenium supplementation (■) and depletion (□). See Figure 1.

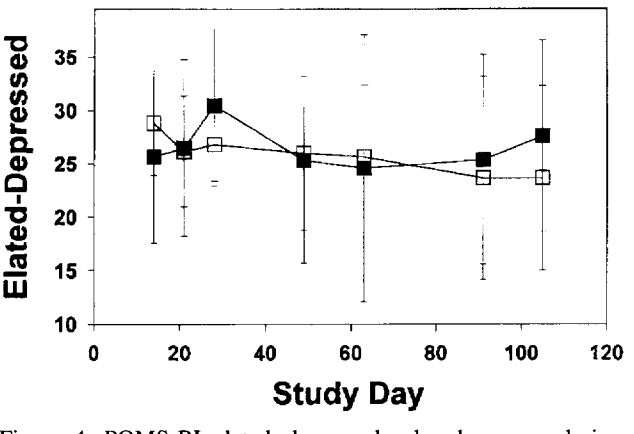

Figure 4. POMS-BI elated–depressed subscale scores during selenium supplementation (■) and depletion (□). See Figure 1.

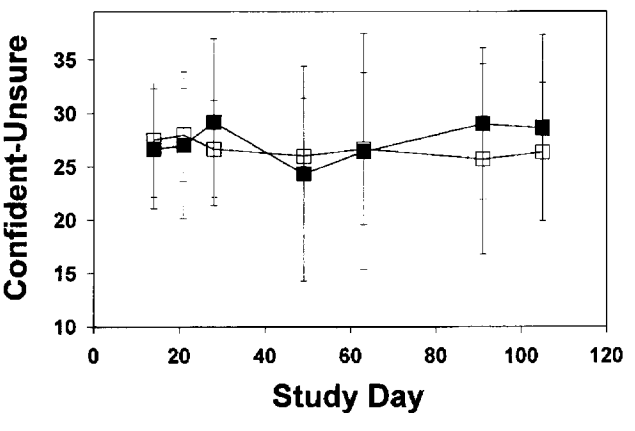

Figure 5. POMS-BI confident–unsure subscale scores during selenium supplementation (■) and depletion (□). See Figure 1.

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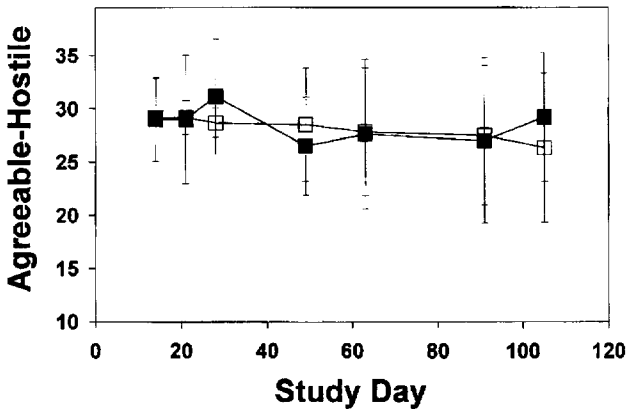

Figure 6. POMS-BI agreeable–hostile subscale scores during selenium supplementation (■) and depletion (□). See Figure 1.

scores in the high-selenium group were significantly related to initial erythrocyte selenium concentration.

Discussion

The results of this study are consistent with some of Benton and Cook's (1991) results and the conclusions they drew. Benton and Cook found that mood scores on the POMS-BI in British women and men with low selenium nutritional status were improved by 5 weeks of selenium supplementation with 100 μg/day; individuals with marginal to adequate selenium nutritional status responded less or not at all to selenium supplementation. The high-selenium diet in the present study represented an average supplementation of about 240 μg/day over our subjects' prestudy selenium intakes, more than twice as much as in the British study, yet it had no observable effect on the POMS-BI mood scores. Since the estimated prestudy selenium intakes of our subjects (48–242 μg/day) were higher than the estimated intakes of the British subjects who did respond to supplemental selenium (28–62 μg/day) and were very similar to those of the nonresponding group of British subjects (63–280 μg/day), the lack of an effect of selenium supplementation on mood in this study does not conflict with Benton and Cook's results and might well have been anticipated.

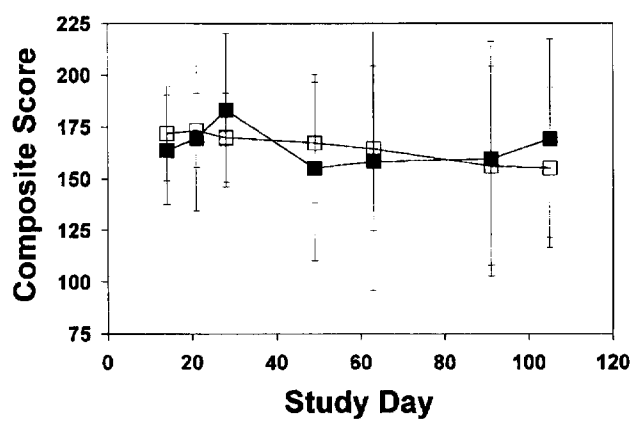

Figure 7. POMS-BI composite scores during selenium supplementation (■) and depletion (□). The mean values of the composite scores (±SEM) are plotted against time during the study. See Figure 1.

Table 1. Correlations Between Changes in Mood and Initial Erythrocyte Selenium Concentrations in Six Subjects Fed a Low-Selenium Diet

POMS-BI scale	Correlation coefficient (r)	Probability of $r = 0$
Clearheaded–confused	0.624	0.18 (NS)[a]
Composed–anxious	0.678	0.14 (NS)
Energetic–tired	0.659	0.15 (NS)
Elated–depressed	0.825	0.043
Confident–unsure	0.372	0.46 (NS)
Agreeable–hostile	0.954	0.003
Composite score	0.751	0.085 (NS)

The changes in the raw POMS-BI subscale and composite scores (day 63/91/105 average minus day 14/21 average) were regressed against the initial erythrocyte selenium concentrations, an indicator of long-term, prestudy selenium nutritional status. A positive correlation indicates that those subjects with lower initial selenium status experienced greater decreases in mood scores during selenium depletion.

[a] NS, not significant ($p > 0.05$).

The methods used to estimate prestudy dietary intakes in the present study (4-day food diaries; mean intake = 101 μg/day) and in Benton and Cook's (1991) study (food frequency questionnaires; mean intake = 72 μg/day) have limitations when used to estimate selenium intakes (Levander 1986; Jørgensen et al 1992). As a consequence, we cannot be certain of the apparent differences in selenium intakes. However, other estimates of typical U.S. and British selenium intakes, based on more reliable methodologies (85 and 43 μg/day, respectively; Combs and Combs 1986) lead to the same inference: that the prestudy selenium status of the subjects in the present study was higher than that of the subjects in Benton and Cook's study. The difference between typical selenium intakes in the United States and Britain is also reflected in the difference between the average British serum selenium concentration (0.092 ± 0.015 μg/mL; Pearson et al 1990) and the average plasma selenium concentration in our subjects (0.128 ± 0.018 μg/mL). Plasma selenium and serum selenium concentrations have been reported to be indistinguishable in the U.S. (Rose et al 1986). The lack of significant direct effects of selenium supplementation or depletion in this study could be due to the higher initial selenium nutritional status in our subjects compared to the subjects who responded to supplementation in Benton and Cook's study. Differences in experimental design may also help explain the much stronger responses to selenium in the British study. Benton and Cook (1991) used a

repeated-measures crossover design with selenium as a within-subject factor in 50 subjects, which should have had greater power to detect an effect of selenium. In contrast, the present study design had no crossover and selenium was a between-subject factor in only 11 subjects.

The present study, however, does support Benton and Cook's (1991) findings that the degree of change observed in the elated–depressed and agreeable–hostile subscales of the POMS-BI was proportional to the subjects' long-term prestudy selenium nutritional status. In the British study, this relationship was seen as a tendency for those subjects with lower prestudy selenium intakes to experience greater increases in mood scores (i.e., more elated and agreeable) with selenium supplementation (negative correlations). In the present study, this dependence on prestudy selenium status was observed as a tendency for subjects with lower initial erythrocyte selenium concentration to experience greater decreases in mood scores (more depressed and hostile) during selenium depletion (positive correlations). The signs of these correlations were opposite in Benton and Cook's study and in this study because the study designs were opposite: Benton and Cook were describing *increases* in mood scores during selenium *supplementation*, whereas we are describing *decreases* in mood scores during selenium *depletion*. In both studies, the elated–depressed and agreeable–hostile subscales responded to changes in selenium intake most strongly in persons with relatively low prestudy selenium status, and less or not at all in persons with higher prestudy selenium status. Thus, both studies describe the same phenomenon, whether the changes were decreases in mood scores during selenium depletion or increases in mood scores during selenium supplementation: the lower the initial selenium status, the greater the change. However, we did not observe a significant correlation between the composed–anxious subscale and selenium status as reported by Benton and Cook (1991), nor did the dependence of the composite mood score on selenium status reach statistical significance in this study.

A preexisting marginal selenium deficiency may be needed to observe an effect of a short-term change in selenium intake on mood. Animal studies have demonstrated that the brain receives a priority supply of selenium during selenium depletion. The brain is the last tissue in the rat to be depleted of selenium when dietary selenium is withheld (Burk et al 1972; Djujic et al 1992) and is the first to be repleted when selenium is resupplied (Behne et al 1988). Therefore, brain selenium levels are maintained at normal levels even when selenium intakes are very low and are increased only slightly by selenium supplementation. As a result, selenium-dependent functions in the brain would be affected by changes in selenium intake only if the brain's selenium status were already low. This could explain why there was no observable effect of selenium depletion on mood in this study. The body's other tissues would have to be depleted of selenium before the brain's priority selenium supply (or any selenium-dependent processes in the CNS) would be impaired. Studies of the kinetics of selenium in humans (Martin et al 1989; Swanson et al 1991) suggest that this degree of depletion would take much longer to achieve than the 84 days during which we monitored our subjects for a change in mood. It is therefore unlikely that CNS concentrations of selenium were greatly changed by the dietary treatments in this study, nor did we attempt to measure selenium in the CNS. The priority supply of selenium to the brain invites speculation that these short-term effects of dietary selenium on mood may be due to actions of selenium at sites other than the CNS. For example, circulating thyroid hormone levels and the concentrations of several blood metabolites were rapidly and significantly changed by the selenium treatments in this study (unpublished observations). These results, as well as extensive biochemical measurements of selenium status in these subjects, will be published elsewhere. Future studies in this area should focus on the mechanisms by which selenium influences mood.

We might have found a stronger indication of an effect of dietary selenium on mood if we had depleted the subjects for a longer period of time or had selected only subjects with a preexisting low selenium status. In addition, a more sensitive indicator of mood changes than the POMS-BI might have revealed more subtle effects of the selenium treatments. The lack of a significant change in the average POMS-BI composite score during the study was unexpected, given the considerable stresses placed on the subjects by the confinement and regimented lifestyle in the metabolic research unit. Although the confinement may have interfered with our ability to detect an effect of selenium intake on mood, there were some key advantages to conducting this study in a metabolic research unit, namely that the nutrient intakes during the study were determined very accurately and with a high degree of confidence; and the design and method of feeding the experimental diets ensured that any differences between the subjects' responses to the high-selenium and low-selenium diets must have been due to these diets' different selenium contents.

Although the results of this study are not definitive, it adds to the growing weight of evidence that selenium is involved in CNS functions and that dietary selenium can affect brain functions, including mood. Furthermore, Benton and Cook's (1991) earlier work indicates the possibility that persons with low selenium status may experience relatively distressed moods and that selenium supplementation could be beneficial in those cases. However, con-

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sidering typical selenium intakes in the United States and the potential for selenium toxicity from uncontrolled supplementation, these studies should not be taken to support the idea that selenium supplementation might promote improvements in mood in individuals consuming a typical U.S. diet. Increasing our subjects' selenium intakes to the maximum safe level produced no benefits in their moods. On the other hand, selenium intakes only 2½ to 3 times greater can be toxic. As a result, selenium supplementation to improve mood cannot be justified in the United States.

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